IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Mundy *et al.*	Art Unit	: 1644
Serial No.	: 10/086,217	Examiner	: Maher M. Haddad
Filed	: February 21, 2002	Conf. No.	: 5114
Title	: METHODS OF TREATING MULTIPLE MYELOMA AND MYELOMA-INDUCED BONE RESORPTION USING INTEGRIN ANTAGONISTS		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY TO ACTION OF NOVEMBER 30, 2006

Claims 86-98 and 100-101 are pending. Claim 90 is withdrawn from consideration.

Applicants respectfully request that the Examiner consider the references cited on the Supplemental Information Disclosure Statement filed September 11, 2006, and indicate that he has done so by returning an initialed copy of the form PTO-1449.

35 U.S.C. § 103

Claims 86-89, 91-98, 100 and 101 were rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 6,692,742 (Nakamura *et al.*) in view of Lokhorst *et al.* (*Blood* 84:2269-2277, 1994) and Masellis-Smith *et al.* (*Cancer Research* 57:930-936, 1997).

The position of the Office appears to rely on the following. Nakamura describes a combination of melphalan and an anti-IL-6 receptor antibody for treatment of multiple myeloma (MM). Lokhorst *et al.* teaches that anti-VLA-4 antibodies inhibited binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma. Lokhorst *et al.* also teaches that inhibition of this cell-cell contact inhibited IL-6 secretion by the LTBMC cells. Masellis-Smith *et al.* teaches that anti-α_4 antibodies that bind $\alpha_4\beta_7$ inhibited MM blood B cell interactions with bone marrow fibroblasts *in vitro*. The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the anti-IL-6 receptor antibodies taught by Nakamura with the anti-VLA-4 antibodies taught by Masellis-Smith *et al.* or Lokhorst *et al.* in a method of treating MM. Applicants respectfully disagree.

None of the references, alone or in combination, teach or suggest treatment of MM by administering an anti-α4 integrin antibody, such as an anti-VLA4 antibody (or an antigen binding fragment thereof), in combination with a chemotherapeutic agent. There is also no suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the teachings of Nakamura, Masellis-Smith and Lockhorst to arrive at the claimed methods. Nakamura *et al.* used anti-IL-6 receptor antibodies (not anti-VLA-4 antibodies) in a mouse model of MM.

Applicants have further presented evidence showing that anti-VLA-4 antibodies and anti-IL-6 antibodies are not interchangeable for treatment of MM (see below). Thus one is not permitted to make the leap that treatment of MM with anti-VLA-4 antibodies in combination with a chemotherapeutic agent is obvious in view of studies that disclose treatment of MM with anti-IL-6 receptor antibodies in combination with a chemotherapeutic agent.

Evidence of why a practitioner of ordinary skill in the art would have believed anti-α4 antibodies, such as anti-VLA-4 antibodies, would not be interchangeable with anti-IL-6 receptor antibodies, or any other agent that inhibits the IL-6 pathway, was explained by Dr. Gregory R. Mundy, an inventor named on the pending application, in a Declaration ("the Mundy Declaration") submitted with the Reply to Office Action on September 11, 2006. Dr. Mundy explained at paragraph 7 of the Declaration that an anti-IL-6 receptor antibody will disrupt a multitude of pathways, as this receptor interacts with at least two different classes of ligands, one class being the gp130 ligands and the other class being the gp80 ligands. Thus, one would not expect that an anti-VLA-4 antibody, which disrupts very different interactions as described below, could substitute for an IL-6 receptor antibody. Dr. Mundy also explained at paragraph 4 of the Declaration that the prior art did not teach that anti-IL-6 antibodies could be used to treat MM. For example, Bataille *et al.* (*Blood* 86:685-691, 1995; cited in the IDS submitted June 21, 2002) taught that anti-IL-6 antibodies were not effective at treating MM. Bataille *et al.* reported that patients with advanced MM did not achieve remission or improved outcome following treatment with murine anti-IL-6 monoclonal antibodies. Dr. Mundy also explained at paragraph 5 of the Declaration that anti-VLA-4 antibodies are believed to work through

mechanisms that are independent of IL-6. Anti-VLA-4 antibodies kill myeloma cells by blocking direct interactions between myeloma cells and normal host cells in the bone marrow. When the myeloma cells cannot attach to the normal host cells, the myeloma cells die. There may be a concomitant decrease in IL-6 levels following administration of anti-VLA-4 (as suggested by the *in vitro* findings of Lokhorst), but this would be a byproduct and not the direct cause of myeloma cell death, nor the reason why the myeloma cells die. Thus in light of the prior art as a whole, and the facts provided by Dr. Mundy, one of skill in the art would not conclude that an anti-VLA-4 antibody could substitute for an IL-6 antibody or an IL-6 receptor antibody, or any other antibody that disrupts the IL-6 pathway, for the treatment of MM.

Even the Nakamura reference relied on by the U.S. Patent and Trademark Office shows that IL-6 receptor antibodies alone were ineffective in the absence of a chemotherapeutic agent for the treatment of MM. See Nakamura at col. 20, lines 23-35; and col. 22, lines 13-20 and 49-53, and Table 2. Thus, even if anti-VLA-4 antibodies inhibit IL-6 (which Examiner reads Lokhorst to suggest), one would not expect IL-6 inhibitory agents to be interchangeable with anti-VLA-4 inhibitory agents to effectively treat MM, whether alone or in combination with any other agent.

The Examiner states at page 5 of the November 30th Office Action that the Mundy Declaration is insufficient to overcome the current rejection under 35 U.S.C. § 103. The Examiner also maintains that

> [t]he idea of combining the references flows logically from the '742 patent teachings methods of treating MM with anti-IL-6 receptor antibodies and melphalan, antibodies which inhibit the biological activity of IL-6, to the Lokhorst *et al.* teachings that monoclonal antibodies directed to the α4-integrin (VLA-4) that inhibit binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma. Furthermore, the antibodies to VLA-4 inhibited the induced IL-6 secretion. Office Action at pages 5-6.

The Examiner disregards Applicants' previous arguments and the statements in the Mundy Declaration, further stating that "the mechanism of action does not have a bearing on the

patentability of the invention if the invention was already known or obvious." Office Action at page 6. Applicants however, note that for a combination of references to render a claimed invention to be obvious, the references must suggest the desirability and thus the obviousness of making the combination, the references must be viewed without the benefit of impermissible hindsight afforded by the claimed invention, and there must be a reasonable expectation of success for achieving the claimed invention. MPEP 2141(II). The Examiner is not permitted to ignore Applicants' evidence showing that VLA-4 inhibitors and IL-6 inhibitors are not interchangeable for the treatment of MM. The ultimate determination on patentability is made on the entire record. *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992). In view of the state of the art at the filing date of the application, and in view of Applicants' evidence indicating that VLA-4 inhibitors and IL-6 receptor inhibitors are not interchangeable for treatment of MM, one of ordinary skill in the art would not have a reasonable expectation of substituting the anti-IL-6 receptor antibodies of Nakamura with anti-VLA-4 antibodies for the treatment of MM even in combination with a chemotherapeutic agent.

In view of the foregoing, Applicants maintain that one of skill in the art would not be motivated to substitute the anti-IL-6 receptor antibodies of Nakamura with anti-VLA-4 antibodies for the treatment of MM, even in view of the disclosures in Lokhorst *et al.* and Masellis-Smith *et al.* There is no suggestion in any of the three references to substitute an anti-VLA-4 antibody for an anti-IL-6 receptor antibody, and in view of the knowledge in the art regarding the different pathways by which each antibody functions, one of ordinary skill in the art would not have a reasonable expectation of successfully treatment MM by making such a substitution. Applicants therefore request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103.

Applicants believe the claims are in condition for allowance, which action is requested.

Enclosed is a petition for extension of time for one month. Please apply the fee of $120, and any other necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 10274-063001.

Respectfully submitted,

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